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Title: Optimal outcome measures for a trial of not routinely measuring gastric residual volume in neonatal care: a mixed methods consensus process

Author list: Chris Gale, Jon Dorling, Barbara Arch, Kerry Woolfall, Elizabeth Deja, Louise Roper, Ashley P Jones, Lynne Latten, Helen Eccleson, Helen Hickey, Nazima Pathan, Jenny Preston, Anne Beissel, Izabela Andrzejewska, Frederic V Valla, Lyvonne N Tume

Corresponding author:
Chris Gale, MBBS, PhD
Neonatal Medicine,
School of Public Health, Faculty of Medicine,
Imperial College London,
Chelsea and Westminster Hospital campus, London
SW10 9NH
Christopher.gale@imperial.ac.uk

Professor Jon Dorling, MBChB, MD
Professor of Pediatrics,
Division of Neonatal-Perinatal Medicine,
Dalhousie University, IWK Health Centre,
5850/5890 University Avenue,
Halifax, NS, Canada, B3K 6R8
Email; jon.dorling@iwk.nshealth.ca

Barbara Arch, **MSc**
Statistician
Liverpool Clinical Trials Centre,
University of Liverpool, a member of the Liverpool Health Partners,
Institute in the Park, Alder Hey Children's Hospital, Liverpool, L12 2AP
Email: barbara.arch@liverpool.ac.uk

Kerry Woolfall, **BA, MA, PhD**
Senior Lecturer
MRC Hubs for Trials Methodology Research Department of Health Services Research
University of Liverpool Block B, Room B112,
1st Floor Waterhouse Building, Liverpool L69 3GL
Email: k.woolfall@liverpool.ac.uk

Elizabeth Deja, BSc MSc PhD
Department of Health Services Research,
University of Liverpool Block B, Room B112,
1st Floor Waterhouse Building, Liverpool L69 3GL
Email: beth.deja@licverpool.ac.uk

Louise Roper, Bsc, MSc, PhD, QHP
Chartered Health Psychologist,
School of Psychology

University of Liverpool
Eleanor Rathbone Building
Bedford Street South
Liverpool
L69 7ZA Email: Louise.Roper@Liverpool.ac.uk

Ashley P Jones, PhD
Senior Statistician
Liverpool Clinical Trials Centre,
University of Liverpool, a member of the Liverpool Health Partners,
Institute in the Park, Alder Hey Children's Hospital, Liverpool, L12 2AP
Email: apjones@liverpool.ac.uk

Lynne Latten, Bsc RD
Advanced Paediatric Dietitian
Nutrition and Dietetics
Alder Hey Children's Hospital
Liverpool, L12 2AP UK
Email: lynne.latten@alderhey.nhs.uk

Helen Eccleson, BSc
Liverpool Clinical Trials Centre,
University of Liverpool, a member of the Liverpool Health Partners,
Institute in the Park, Alder Hey Children's Hospital, Liverpool, L12 2AP
Email: Helen.Eccleson@liverpool.ac.uk

Helen Hickey, PGDip
Liverpool Clinical Trials Centre,
University of Liverpool, a member of the Liverpool Health Partners,
Institute in the Park, Alder Hey Children's Hospital, Liverpool, L12 2AP
Email: h.hickey@liverpool.ac.uk

Dr Nazima Pathan FRCPCH PhD
Consultant in Paediatric Intensive Care, Cambridge University Hospitals NHS Trust
University Lecturer in Paediatrics, University of Cambridge
Clinical Research Associate, Kings College, Cambridge
Email: np409@medschl.cam.ac.uk

Jenny Preston, BA (Hons)
University of Liverpool, Dept. of Women's and Children's Health,
Institute of Translational Medicine (Child Health),
Alder Hey Children's NHS Foundation Trust, Liverpool, L12 2AP
Email: Jennifer.Preston@liverpool.ac.uk

Anne Beissel, MD
Consultant Neonatologist
Hôpital Femme Mère Enfant,
Hospices Civils de Lyon, Lyon-Bron, France
Anne.Beissel@chu-lyon.fr

Izabela Andrzejewska RN MSc
Neonatal Research nurse
Chelsea and Westminster NHS Trust
London SW10 9NH
Izabela.Andrzejewska@chelwest.nhs.uk

Frederic V Valla, MD PhD
Consultant in Pediatric Intensive Care
Paediatric intensive care unit, Hôpital Femme Mère Enfant,
CarMEN INSERM UMR 1060 Hospices Civils de Lyon, Lyon-Bron, France
Frederic.Valla@chu-lyon.fr

Dr Lyvonne N Tume, RN PhD
Reader in Child Health,
University of Salford, Manchester UK
Frederick Road Campus, M6 6PU
Email: l.n.tume@salford.ac.uk

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Lyvonne Tume is an NIHR HTA panel member.

Selection of outcome measures for a trial of not routinely measuring gastric residual volume in neonatal care: a mixed methods consensus process

Abstract (250 words)

Background: Routine measurement of gastric residual volume to guide feeding is widespread in neonatal units but not supported by high-quality evidence. Outcome selection is critical to trial design.

Objective: To determine optimal outcome measures for a trial of not routinely measuring gastric residual volume in neonatal care.

Design: A focused literature review; parent interviews; modified two-round Delphi survey and stakeholder consensus meeting.

Participants: Sixty-one neonatal healthcare professionals participated in an eDelphi survey; 17 parents were interviewed. 19 parents and neonatal healthcare professionals took part in the consensus meeting.

Results: Literature review generated 14 outcomes and parent interviews contributed eight additional outcomes; these 22 outcomes were then ranked by 74 healthcare professionals in the first Delphi round where four further outcomes were proposed; 26 outcomes were ranked in the second round by 61 healthcare professionals. Five outcomes were categorised as ‘consensus in’, no outcomes were voted ‘consensus out’. ‘No consensus’ outcomes were discussed and voted on in a face-to-face meeting by 19 participants, where four were voted ‘consensus in’. The final nine consensus outcomes were: mortality, necrotising enterocolitis, time to full enteral feeds, duration of parenteral nutrition, time feeds stopped per 24 hours, healthcare associated infection; catheter associated bloodstream infection, change in weight between birth and neonatal discharge and pneumonia due to milk aspiration.

Conclusions and relevance: We have identified outcomes for a trial of no routine measurement of gastric residual volume to guide feeding in neonatal care. This outcome set will ensure outcomes are important to healthcare professionals and parents.

250words

Introduction

Heterogeneity in outcome selection limits evidence synthesis and is a problem in neonatal care[1] where meta-analyses rarely provide conclusive recommendations[2]. Neonatal trial outcomes are often not meaningful to parents and patients[3,4]; selection of clinically relevant outcomes that are important to parents and patients is key to improving uptake of research into practice[5]. A solution is the development and application of core outcome sets, important outcomes identified by key stakeholders using robust consensus methods[6]. The Core Outcomes In Neonatology (COIN) set has been identified[7] and should be the minimum[8] standard for neonatal effectiveness trials, however research questions often measure additional specific outcomes; selection of these should also involve key stakeholders and robust methodology.

This study is part of a larger National Institute for Health Research (NIHR) funded mixed methods feasibility study (GASTRIC) to determine whether it was possible to conduct a future trial comparing no routine gastric residual volume measurement with routine gastric residual volume measurement to guide feeding in neonatal care[9].

Methods

A four stage mixed method study followed established methodology for identification of core outcomes for trials[6], March 2018 - April 2019:

1. A focused literature review of outcomes reported in clinical trials and observational studies of gastric residual volume measurement in critically ill adults, children or neonates: Databases were searched (Medline, CINAHL, Proquest) in March 2018 by LNT using the search terms: ‘gastric residual’ and ‘gastric aspirate’ in critically ill patients. Outcomes were extracted from identified studies.

2. Parent interviews: Qualitative researchers (LR and ED) recruited English-speaking parents of children that received neonatal care in the last three years via social media,

national networks, word of mouth and a newspaper advertisement. A participant information sheet listing potential outcomes identified from the focused literature review was emailed to parents to read prior to interview. Based on previous research[10] it was anticipated that 10-15 parents would be recruited to reach data saturation point[11]. Interviews explored views on the proposed GASTRIC trial and which outcomes parents felt would be important. Content analysis[12] was used to identify outcomes to inform the subsequent Delphi study.

3. Delphi Study: A modified 2-round Delphi[13] e-survey was developed from the literature review and the parent interviews (Supplementary File 1) and pilot tested for clarity and face validity with ten healthcare professionals and the study team, and input into DelphiManager[14]. Nurses, doctors, pediatric surgeons and dietitians working in neonatal units were invited to take part via email through professional networks. The target number of respondents was 100 to ensure representation from key stakeholder groups with understanding of relevant issues, and consistent with previous core outcome sets[6]; automated reminders were sent weekly.

Round 1 summarised previous trial designs and outcomes used, and listed a set of outcomes to score using a 9-point Likert scale as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group[15], 1–3 signifying 'not important', 4–6 'important but not critical' and 7–9 'critical'. Participants were able to comment and asked to suggest additional relevant outcomes. Outcomes were listed alphabetically to avoid bias due to the order displayed. After Round 1 the study management group reviewed additional suggested outcomes and added distinct outcomes to the second round. In Round 2, participants were presented with descriptive statistics and histograms of Round 1 scores for each outcome by stake-holder group, asked to re-score these outcomes, to score additional outcomes suggested in Round 1, and to specify a single primary outcome.

The Round 2 scores were used to formulate consensus statistics for each outcome overall and by stakeholder group, using pre-defined cut-offs for 'Consensus In' (≥70% participants scoring 7 to 9 AND <15% participants scoring 1 to 3 in each stakeholder group), 'Consensus Out' (≥70% participants scoring 1 to 3 AND <15% participants scoring 7 to 9 in each

stakeholder group), 'No consensus' (anything else). Consensus thresholds were defined *a priori* consistent with published guidance and previous studies[6].

4. Face-to-face consensus meeting: Parents, clinical trial methodologists and neonatal healthcare professionals were invited to review the results of the mixed-methods study, vote on outcomes that did not reach consensus in the Delphi survey and discuss future trial feasibility and design. An independent facilitator led the meeting. Voting results were summarised using the same methodology as described for the Delphi.

Ethics approval: University of the West of England, April 2018 (REF HAS.18.04.144).

Results

Literature review

The focused literature review identified six studies, one in children[16], three in adults[17-19] and two in preterm neonates[20,21]. Reported outcomes were summarised (Table 1). Incidence of ventilator associated pneumonia was not reported in the neonatal studies and therefore not included in the neonatal Delphi, gastrointestinal morbidity was separated into vomiting and diarrhea, generating 14 items from the literature review. Figure 1 shows the generation of outcomes across the study.

Parent-important outcomes

Seventeen parents of 19 children (two mothers had twins) who received neonatal care in 21 hospitals were interviewed. Interviews took place on average 11 months (range 0.8 - 37 months) after neonatal admission. Reasons for neonatal care were preterm birth (n=18) and meconium aspiration syndrome (n=1). Parents split 'long-term neurodevelopment' into long-term hearing loss, problems with vision, problems with cognition and motor problems (such as cerebral palsy), and proposed four further outcomes: time from birth to nasogastric tube removal, total length of time on any respiratory support, brain injury on imaging, and healthcare associated infections.

Delphi Study

In November 2018, healthcare professionals at all 184 neonatal units in England, Scotland and Wales were contacted via email; 76 individuals registered for the survey, 74 went on to score 22 outcomes in Round 1, and of these, 61/74 (80%) went on to complete Round 2. Four additional outcomes were suggested by respondents in Round 1: change in head circumference, incidence of pneumonia due to aspiration of feeds; incidence of catheter associated bloodstream infection, time to oral feeding; 26 outcomes were included in Round 2. 76% (46/61) of respondents changed their score for at least three outcomes from Round 1 to Round 2. There was no evidence of attrition bias between rounds; the 13 healthcare professionals that only took part in Round 1 had similar views to those who took part in both rounds (supplemental figures). After Round 2 'consensus in' was achieved for five outcomes: mortality; incidence of necrotising enterocolitis; time to full enteral feeds; duration of parenteral nutrition; time feeds stopped per 24-hour period. No outcomes were voted 'consensus out'. Outcomes scored in Round 2 are shown in Table 2 with the outcome source and consensus status.

Respondents were asked their choice of primary outcome for a future trial: 48/61 (79%) respondents suggested at least one; the most common were incidence of necrotising enterocolitis (24/61; 39%) and time to full enteral feeds (18/61; 30%).

Consensus meeting

Nineteen participants (1 charity representative; 1 clinical trialist/methodologist; 2 neonatal dietitians; 5 neonatal doctors; 7 neonatal nurses; 1 paediatric surgeon; 2 parents) attended the consensus meeting on 1st April 2019, representing 14/184 (8%) of UK neonatal units, three universities and the charity Bliss. Some had participated in the Delphi study. At this meeting there was discussion and voting on the 21 outcomes that did not reach consensus in the Delphi. Using the same scoring criteria as the Delphi survey, four items were voted 'consensus in', four were voted 'consensus out' and 13 failed to reach any consensus (Table 3). Nine consensus outcomes for a future trial are presented in Table 4.

Discussion

This study reports a set of outcomes identified as important by healthcare professionals and parents for a trial comparing no routine measurement of gastric residual volumes in neonatal care to routine measurement. This study-specific outcome set was developed following a robust process with involvement of key stakeholder groups. This is one of the few studies to apply such methods to outcome selection in neonatal or paediatric care. Poor outcome selection is increasingly recognised as a source of research waste[1,22]. The use of study-specific outcome sets in conjunction with relevant Core Outcome Sets, such as COIN[7], will ensure trials support evidence synthesis, are relevant to parents and inform clinical practice.

Gastric residual volume is a measurement of the volume of the entire stomach contents from aspirating with a syringe, and is distinct from the aspiration of a small volume of gastric fluid for pH testing to confirm gastric tube position. Routine measurement of gastric residual volume commonly informs feeding decisions in neonatal units in the UK[23] and internationally. The rationale underpinning this is to assess 'feed tolerance' and to predict, and potentially prevent, necrotising enterocolitis by withholding enteral feeds[24,25]. However, there is minimal evidence to support routine measurement of gastric residual volumes in neonatal care. A recent single-centre trial found that avoiding routine measurement of gastric residual volumes may be beneficial, leading to higher weight gain and shorter length of stay[26], however trials to date have not had power to evaluate the relationship between gastric residual measurement and necrotising enterocolitis[26,27]. Despite potential harms such as mucosal injury, and evidence that gastric residual volume is an inaccurate measure of gastric contents[28], routine assessment of gastric residual volumes is engrained in neonatal care[29]. This study was commissioned by the United Kingdom NIHR as part of a wider piece of work to evaluate the feasibility of a multi-centre trial examining no routine measurement of gastric residual volumes. This study identifies a set of outcomes for such a trial which comprise uncommon but severe events (mortality, necrotising enterocolitis, pneumonia secondary to milk aspiration and infection) and nutritional outcomes (time to full enteral

feeds, days of parenteral nutrition, number of times that feeds are stopped, change in weight). While there is some overlap with core outcomes identified for neonatal research generally[7], this study specific outcome set more closely targets nutritional outcomes – highlighting the importance of using general core outcome sets in conjunction with trial specific consensus processes that involve parents and patients.

Previous neonatal trials have targeted nutritional outcomes (time to achieve full enteral feeds) as the primary outcome. Although these studies have reported necrotising enterocolitis, event rates have been low. Healthcare professionals are highly concerned about adverse events[30] and may fear these more than they value improved outcomes. This study confirms that the adverse outcome necrotising enterocolitis is key across all stakeholder groups for this clinical question. The incidence of necrotising enterocolitis is low among all but the most preterm infants[31] and therefore any trial seeking to demonstrate superiority or non-inferiority for such an outcome will require high numbers and multiple sites. Previous trials have not had sufficient size to detect differences in necrotising enterocolitis, which may in part explain why routine measurement of gastric residuals remains entrenched in neonatal practice single-centre trials that indicate it is detrimental.

Strengths include a pre-registered approach that identified trial outcomes for the Delphi survey and consensus meeting from both previous research and parents with experience of neonatal care. Limitations include the incomplete participation of UK neonatal units in the Delphi survey, although the response rate of 40% is in keeping with other surveys. The consensus process was deliberately limited to UK neonatal professionals and parents to determine the feasibility of a UK trial, which limits generalisability to other healthcare settings. Some identified outcomes overlap or are not well defined in neonates, and will require refinement prior to any future trial. We had only limited participation in the Delphi from neonatal dieticians, however this group was well represented in the final consensus meeting. We did not include parents in the Delphi survey as asking for parental views on

outcomes at interview and involving them in the final consensus meeting were felt to be the most appropriate ways to gain meaningful input from this group.

Conclusions

We describe development of an outcome set for a trial comparing no routine gastric residual volume measurement with routine measurement to guide feeding in neonatal care. This was identified though a consensus approach involving parents and neonatal clinical stakeholder groups. The use of such outcomes increases the likelihood that future trial results are both meaningful to parents/patients and are implemented in clinical practice.

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Statement of authorship

L Tume, C Gale and J Dorling equally contributed to the conception and design of the research; H Hickey, K Woolfall, E Deja, L Roper, A Beissel, F Valla, B Arch contributed to the design of the research; H Eccleson, J Preston, I Andrzejewska, N Pathan, L Latten, B Arch and E Deja contributed to the acquisition and analysis of the data; E Deja and L Roper conducted qualitative interviews; E, Deja, B Arch, AP Jones, L Tume, C Gale and J Dorling contributed to the interpretation of the data; and C Gale, B Arch and L Tume drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Figure 1: Generation of outcomes across different stages of the study

Table 1: Outcomes identified in previous studies of gastric residual volume measurement

Outcome	Patient population
1. Intensive care unit length of stay	All
2. Hospital length of stay	All
3. Length of invasive ventilation	All
4. Occurrence of ventilator associated pneumonia	Adult and paediatric
5. Achievement of predicted energy goals using various definitions: Proportion of patients achieving 100% Cumulative calorie deficit over 7 days Ratio of prescribed/achieved energy target Enteral feeding 'adequacy' Median daily volume of feed given Percentage of predicted energy requirement achieved per day Time to achieve full feeds for preterm neonates (120ml/kg and 150ml/kg/day)	Adult, paediatric and neonatal
6. Occurrence of necrotising enterocolitis	Neonatal and paediatric
7. Incidence of gastro-intestinal intolerance: vomiting, diarrhea, abdominal distention, feed intolerance, gastro-esophageal reflux	Adult and paediatric
8. Nursing time spent measuring gastric residual volumes	Adult
9. Change in weight from admission to discharge	Neonatal and paediatric
10. Change in length from admission to discharge	Neonatal
11. Days of parenteral nutrition	Neonatal
12. Days with a central venous catheter in place to deliver parenteral nutrition	Neonatal
13. Time feeds stopped per 24-hour period	Adult
14. Survival	All

Table 2: Percentage of participants that scored 7, 8 or 9 for each outcome scored in Round 2 of the Delphi study, by stakeholder group

Outcome	Outcome source	Doctors (n=40)	Nurses (n=18)	Dietitians (n=3)	All (n=61)	Consen-sus status
Mortality	LR	*100%	*100%	*100%	**100%	In
Incidence of necrotising enterocolitis	LR	*100%	*94.4%	*100%	**98.4%	In
Time from start of enteral feeding to achieve full (150ml/kg/day) enteral feeds	LR	*92.5%	*88.9%	*100%	**91.8%	In
Healthcare associated infections	Parents	*87.5%	*88.9%	66.7%	*86.9%	None
Days on parenteral nutrition	LR	*77.5%	*94.4%	*100%	**83.6%	In
Incidence of catheter-associated blood stream infection	DR1	*85%	*70.6%	66.7%	*80%	None
Time feed stopped per 24 hour period	LR	*70%	*83.3%	*100%	**75.4%	In
Change in weight (growth) between birth and neonatal unit discharge	LR	*75%	*77.8%	66.7%	*75.4%	None
Days of central venous line access	LR	*75%	*72.2%	66.7%	*73.8%	None
Length of stay in hospital	LR	45%	*72.2%	*100%	55.70%	None
Incidence of pneumonia due to milk aspiration	DR1	37.5%	*76.5%	66.7%	50%	None
Length of stay neonatal unit	LR	35%	*72.2%	66.7%	47.5%	None
Long term outcomes: Problems with mobility like cerebral palsy	Parents	45%	50%	33.3%	45.9%	None
Long term outcomes: Problems with cognition	Parents	35%	38.9%	33.3%	36.1%	None
Gastro-intestinal morbidity: Vomiting	LR	30%	61.1%	*100%	42.6%	None
Change in head circumference between birth and neonatal unit discharge	DR1	42.50%	23.50%	*100%	40%	None
Change in length (growth) between birth and neonatal unit discharge	LR	42.50%	27.80%	66.70%	39.30%	None
Brain injury on imaging	Parents	25%	33.30%	33.30%	27.90%	None
Time to oral feeding	DR1	27.50%	23.50%	33.30%	26.70%	None
Length of time invasive ventilation	LR	12.5%	50%	66.7%	26.2%	None
Long term outcomes: Hearing loss	Parents	15%	27.80%	33.30%	19.70%	None
Long term outcomes: Problems with eyesight	Parents	15%	27.80%	33.30%	19.70%	None
Nursing time spent measuring gastric residual volumes	LR	5%	27.80%	66.70%	14.80%	None
Gastro-intestinal morbidity: Diarrhoea	LR	5%	27.80%	33.30%	13.10%	None
Total length of time respiratory support (invasive and non-invasive)	Parents	2.50%	27.80%	0%	9.80%	None
Time to nasogastric tube removal	Parents	10%	5.60%	0%	8.20%	None

* 'Consensus in' criteria were met: ≥70% scored 7, 8 or 9 and <15% scored 1, 2 or 3;
** 'Consensus in' criteria met in all groups;
† 'Consensus out' criteria were met: ≥70% scored 1, 2 or 3 and <15% scored 7, 8 or 9 [NB: None found];
†† 'Consensus out' criteria met in all groups;
Source of outcome: LR Literature review; DR1 Delphi Round 1

Table 3: No-consensus items voted on at consensus meeting

Outcome	Consensus status
Healthcare associated infections	In
Incidence of catheter-associated blood stream infection	In
Change in weight between birth and neonatal unit discharge	In
Incidence of pneumonia due to milk aspiration	In
Change in head circumference between birth and neonatal unit discharge	No Consensus
Brain injury on imaging	No Consensus
Gastrointestinal morbidity: Vomiting	No Consensus
Length of stay hospital	No Consensus
Length of stay neonatal unit	No Consensus
Length of time receiving invasive ventilation	No Consensus
Long term outcomes: Hearing loss	No Consensus
Long term outcomes: Problems with vision	No Consensus
Long term outcomes: Problems with cognition	No Consensus
Long term outcomes: Brain injury on imaging	No Consensus
Long term outcomes: Motor problems	No Consensus
Time to oral feeding	No Consensus
Total length of time receiving respiratory support (invasive and non-invasive)	No Consensus
Change in length (growth) between birth and neonatal unit discharge	Out
Gastrointestinal morbidity: Diarrhoea	Out
Nursing time spent measuring gastric residual volume	Out
Time to nasogastric tube removal	Out

Table 4: Final nine outcomes gaining consensus for a trial of no gastric residual volume measurement

Mortality
Incidence of necrotising enterocolitis
Time from start of enteral feeding to achieve full (150ml/kg/day) enteral feeds
Days on parenteral nutrition
Time feed stopped per 24 hour period
Healthcare associated infections
Incidence of catheter-associated blood stream infection
Change in weight between birth and neonatal unit discharge
Incidence of pneumonia due to milk aspiration

What is already known on this topic

1. Routine measurement of gastric residual volume to guide feeding is widespread in neonatal units worldwide, but not supported by high-quality evidence
2. Adequately powered and methodologically robust randomised trials would provide evidence about risks and benefits of routine measurement of gastric residual volume in neonatal care
3. Selection of trial outcomes that are relevant to health professionals, parents and patients is key to improving the quality and implementation of research

What this study adds

1. We have identified outcomes for a trial of no routine measurement of gastric residual volume to guide feeding in neonatal care.
2. Consensus outcomes included: mortality, necrotising enterocolitis, time to full enteral feeds, duration of parenteral nutrition, time feeds stopped per 24 hours, healthcare associated infection
3. Use of this outcome set in trials of no routine measurement of gastric residual volume will ensure outcomes are important to clinicians and parents.

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